Molecular Pathways

ERK1/2 and p38α/β signaling in tumor cell quiescence: opportunities to control dormant residual disease.

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Running title: p38 signaling and dormancy.
Abstract

Systemic minimal residual disease after primary tumor treatment can remain asymptomatic for decades. This is thought to be due to the presence of dormant disseminated tumor cells (DTCs) or micrometastases in different organs. DTCs lodged in brain, lungs, livers and/or bone are a major clinical problem because they are the founders of metastasis, which ultimately kill cancer patients. The problem is further aggravated by our lack of understanding of DTC biology. In consequence there are almost no rational therapies to prevent dormant DTCs from surviving and expanding. Several cancers including melanoma as well as breast, prostate, and colorectal carcinomas undergo dormant periods before metastatic recurrences develop. Here we review our experience in studying the crosstalk between ERK1/2 and p38α/β signaling in models of early cancer progression, dissemination and DTC dormancy. We also provide some potential translational and clinical applications of these findings and how some currently used therapies might be useful to control dormant disease. Finally, we draw caution on the use of p38 inhibitors currently in clinical trials for different diseases as these may accelerate metastasis development.
**BACKGROUND**

*Origin and fate of disseminated tumor cells DTCs.* The inherent complexity of metastasis biology has proven difficult to unravel (1). Metastasis treatment with conventional chemotherapy is mostly ineffective because when diagnosed these lesions are already large (i.e. $10^{10}$-$10^{11}$ tumor cells (2)) and heterogeneous (3). Moreover, the biological and genetic divergence between primary tumors and metastasis (4) further complicates treatment. Thus, a constant “catch-up” game is played with the robust genetic and epigenetic resourcefulness of metastases, where treatments are given sequentially until lesions become completely refractory.

Clinical tumor dormancy is the asymptomatic period between the time of primary tumor detection and treatment and its local or distant metastatic relapse. However, this time does not necessarily imply the presence of dormant disease and could be explained simply by tumor doubling times (1). This argues for the need of better markers to define truly dormant residual disease. We distinguish tumor cell dormancy (i.e. of disseminated disease) from tumor latency that is mostly used to define the time from the carcinogenic event to the clinical diagnosis of the primary tumor (5). Dormancy of a micrometastatic mass where the proliferating population is balanced by a dying one may be due to failure to induce an angiogenic switch and/or to immune cell-mediated mechanisms (5). In contrast cellular tumor dormancy, which most likely explains solitary DTC dormancy can be explained by quiescence programs (a reversible growth arrest state) in which DTCs remain non-productive until changes in microenvironment (i.e. lung, liver, bone marrow) signals activate them to resume growth (6). These scenarios can unfold soon after primary tumor treatment (1-2 years) or decades later (6).

By the time of diagnosis a large number of patients have already disseminated disease lodged in target organs in the form of solitary DTCs (1). These DTCs can be found in secondary organs such as liver and sentinel lymph nodes (LN) as well as in bone marrow (BM) (7). DTCs are commonly studied in bone marrow aspirates due to easy access to this compartment. However, the bone is not the only place where they reside. In fact, DTCs are most likely in multiple organs simultaneously and sampling of the BM provides a snapshot of what their behavior and characteristics might be systemically. It is widely accepted that these single DTCs are the seeds for later tumor metastases. It is proposed that circulating tumor cells (CTCs) (i.e. isolated from peripheral blood (8)) will become DTCs when lodged in a secondary tissues (e.g. lung, liver), but for the most part these are short-lived tumor cells in circulation that provide primarily a snapshot of recently intravasated tumor cells (9) and therefore of primary or secondary tumor masses that shed cells. But once the tumor is surgically removed CTC numbers commonly decrease, while DTCs can be detected for long periods (1). Thus, these cells carry information on both their origin and how the target organ affects them. Unfortunately,
because DTC biology is poorly understood, we currently miss the opportunity to eradicate these tumor cells and prevent metastasis (5). Further, because non-proliferative DTCs (see below) may evade conventional therapies (5), a completely different approach might be needed to eradicate these cells.

Dormancy of DTCs might be explained by two complementary hypotheses. These propose that during cancer progression dissemination represents either early or late events. The first is supported by the frequent detection of BM DTCs in patients carrying non-invasive lesions (e.g., ADH or DCIS) (4). In MMTV-Neu (Neu) mice, where p38 antagonizes tumor development (10), pre-malignant lesions contained micro-invasive cells and dissemination to lungs and BM occurred early (11). In uveal melanoma, a cancer with 50% incidence of late liver recurrence (>10 years) in humans (12), analysis of tumor doubling times led to the conclusion that dissemination had occurred at least 5 years before diagnosis. In a mouse model of uveal melanoma (13) it was shown that dissemination occurred early and dormant DTCs (i.e. growth-arrested) were commonplace. In a *D. melanogaster* CSK null cancer model, early dissemination required Src activation without loss of E-cadherin or apparent EMT induction (14). Early DTCs might carry robust survival signals but still lack key genetic and epigenetic changes to sustain proliferation (11). In consequence, prolonged growth arrest with interspersed division might explain the clinical dormancy during which slow accumulation of genetic and/or epigenetic alterations give rise to malignant DTCs and relapse. For an excellent recent review see the article by Klein (1). Finally, late DTCs that progressed in the primary tumor may reprogram into quiescence and co-exist with early DTCs in patients with invasive cancers (5) that can display long metastases-free periods. This might be regulated by metastasis suppressor genes (MSG) that can respond to microenvironmental stress responses (15). There is a growing number of these genes that selectively affect growth at secondary sites and they include KISS1, MKK4, MKK6, BHLHLB3/Sharp-1 and Nm23-H1 among others (15). For a comprehensive review see (15). These genes may inhibit metastasis by inducing DTC growth arrest, preventing the formation of overt metastases (15). Interestingly, MKK4 and MKK6 are upstream activators of p38 (15), BHLHB3 is a target of p38 required for quiescence induction (16) (see below) and Nm23-H1 appears to function via the downregulation of EDG2 LPA receptor a strong activator of ERK1/2 (17). Thus, it seems that different mechanisms might converge on the regulation of the [ERK/p38] signaling ratio. Here we discuss the role of p38 signaling in controlling early breast cancer progression and early dissemination and how the [ERK/p38] signaling ratio can regulate reprogramming of aggressive tumor cells into quiescence.
THE PATHWAY: STRESS SIGNALING THROUGH p38α/β. The mitogen-activated protein kinases (MAPKs) belong to a family of highly conserved intracellular kinases that transduce extracellular signals relayed by surface receptors or various types of damage (18). Three subfamilies exist in mammals and include ERK, JNK and p38 kinases. Four isoforms (α, β, γ and δ) constitute the p38 family. They were initially identified as modulators of inflammatory responses where they regulate the expression of different cytokines (18). Furthermore, they were also found to play important roles in cell proliferation by activating G1/S and G2/M checkpoints (18). It is also known that p38 can suppress transformation of normal epithelial cells (19-21) and it activates anoikis, which prevents aberrant localization of epithelial cells (19). In addition, p38α can promote growth arrest by downregulating cyclin D1 (21) and by activating the p53 to p21 and/or p16 to Rb pathways (22, 23) among others (24). Further, p38α inhibits transformation by sensing oncogene-induced oxidative stress (25), inactivation of p38α facilitates ErbB2-induced mammary tumorigenesis in vivo (10, 22) and ~18% of human primary breast carcinomas display Wip1/PPM1D (a p38 phosphatase) amplification (10, 22). Thus, Wip1 inhibitors (26) might be useful to restore p38α signaling in tumors. Activation of p38α can also cooperate with reduced ERK1/2 mitogenic signaling to induce quiescence of tumor cells (Fig1) (16). Furthermore, as mentioned above metastasis suppressor genes (i.e. MKK4) can act upstream or downstream of p38 activation (27). Despite these advances, how p38α signaling is spatio-temporally regulated during cancer progression to suppress early tumorigenesis, dissemination or to prevent DTCs from becoming overt metastasis is still unclear.

P38α/β REGULATES EARLY BREAST CANCER PROGRESSION AND DISSEMINATION. Activation of p38α/β is a barrier to mammary tumor progression (10). We recently pinpointed this function of p38α during mammary morphogenesis by demonstrating that it activates anoikis of centrally located luminal ductal cells during mammary acinar development (28). This work revealed that p38α inhibited ERK1/2 possibly by regulation of PP2A and MKP phosphatases (29) and activated ATF-2 to induce c-Jun. Then, jointly, these TFs along with reduced ERK1/2 activity induced the pro-apoptotic factor BimEL in cells devoid of integrin-mediated attachment (28). This triggered anoikis and lumen formation. Remarkably, this leads to the formation of structures reminiscent of DCIS (28). In MMTV-Neu mice, where dissemination occurs during pre-malignant stages (11), p38α/β inhibition accelerated pre-malignant lesion development, lumen occupancy and local migration of both the epithelial and myoepithelial cells (28). Histological analysis of normal FVB or MMTV-Neu mammary glands showed enhanced ERK1/2 phosphorylation and reduction of E-cadherin levels in luminal epithelial cells (unpublished data) when p38 was inhibited. This was sufficient to enhance dissemination as p38α/β
inhibition more than doubled the number of disseminated tumor cells (Her2+, CK8/18+ (11)) in the BM (unpublished data). These data suggest that p38 signaling might simultaneously prevent early cancer progression (18, 28) and early dissemination almost simultaneously. We further propose that early DTCs might retain functional p38 signaling and perhaps metastasis suppressor gene expression which restricts colonization of distant organs by contributing to clearance (via anoikis? (19)) or dormancy via quiescence (Fig1) (16). Thus, maintaining p38 signaling in disseminated malignant cells might prevent clinical relapse.

**DORMANCY INDUCED BY AN ERK^{LOW}/P38^{HIGH} SIGNALING RATIO.**

*Dormancy of a tumor mass vs. dormancy of tumor cells.* The lack of proliferation markers in surviving DTCs in patients and data from experimental systems suggest that DTC dormancy might be controlled by mechanisms of quiescence (5), a reversible growth arrest that can be brought about by different signals (30). Further, specific transcription factors (TFs) can prevent quiescent cells from entering differentiation or senescence (an irreversible growth arrest that can lead to cell death or clearing by phagocytic cells) (30), two cellular end points that tumor cells can evade (31). Angiogenic dormancy or immune system-mediated tumor mass dormancy might also be of importance in certain contexts (32, 33). Interestingly, anti-angiogenesis and quiescence programs might be coupled, as there are many common regulated genes in angiogenic dormancy (32) and quiescence models (16). Recent studies also suggest that immune cell-mediated dormancy might require the induction of tumor cell growth arrest as well (13, 34).

*ECM and stress signaling regulation of dormancy.* The seed and soil theory would support the idea that the interactions DTCs establish with target organ ECM, or stromal cells (35) could determine growth vs. dormancy and dictate the distinct and predictable pattern of metastasis (5). Studies on breast cancer cell lines selected for growth in the bone for example show that these cells selectively regulate gene expression programs that favor organ specific colonization (36). In squamous carcinoma cells (HEp3) it was shown that reduced urokinase receptor expression α5β1-integrins made these cells incapable of binding efficiently to fibronectin (Fig1) (37). This resulted in reduced FAK and EGFR signaling but also in p38 activation. Other groups have corroborated these findings showing that loss of β1-integrin or FAK signaling in the mammary epithelium or in intravenously delivered mouse breast cancer cells can also induce dormancy and that Src MLKC signaling can prevent dormancy onset (5, 38). It was also shown that activation of p38 by blockade of adhesion signaling resulted in further inhibition of ERK1/2 while also activating a stress adaptive response known as the unfolded protein response (UPR) (16, 39). Together, these signals favored survival and
acquisition of a dormant phenotype by HEp3 (D-HEp3) cells (40) that was characterized by a deep G0-G1 arrest associated with p21, p27, p18 and p15 induction and only observed in vivo ((16) and unpublished results) (Fig1). Activation of p38α/β induced at least 3 TFs, p53 (R213Qmut), BHLHB3/41/Sharp1, NR2F1 and inhibited the expression of c-Jun and FOXM1, two G1-S transition TFs (16). Importantly, the R213Q mutation in p53 does not affect its ability to induce G0/G1 arrest but it prevents the induction of senescence or apoptosis ((16) and unpublished results). This combinatorial regulation of TFs is responsible for the quiescence program in dormant tumor cells in vivo (16). But are these programs activated in DTCs and what signals elicit these quiescence and stress resistance programs?

Therapy- and microenvironment-induced dormancy. Residual tumor cells that survive chemotherapy might respond to this stress by entering quiescence. Modeling this phenomenon in multiple myeloma revealed that tumor cells that survive bortezomib treatment enter quiescence due in part to activation of an UPR (41). Bortezomib-induced quiescent MM cells were eradicated by preventing eIF2α dephosphorylation using the GADD34-PP1c inhibitor salubrinal (41). Thus, even quiescent tumor cells could be killed ((41, 42) and see below). Alternatively, the target organ microenvironment activates DTC dormancy (5). For example, in prostate and breast cancer bone metastasis occur at a frequency of 10-30% (43-45). However, detection of BM DTCs is much higher (>50% of patients) (46, 47), suggesting that not all DTCs are productive and that metastasis could be blocked or delayed. Furthermore, spontaneous metastases in mouse models (xenografts/immune deficient or transgenic/immune competent) also show organ specific growth that does not always follow DTC presence (Fig1) (11, 48). For example, in MMTV-Neu transgenic mice, BM DTCs are readily detected but bone metastases never develop (11). However, if the mice were irradiated (11) now DTCs expanded in the BM (but not in other sites), suggesting that loss or gain of specific signals only after BM remodeling activated DTCs to proliferate. Previous studies have shown that HEp3 primary tumor cells spontaneously disseminated to lungs, lymph nodes (48), liver and bone marrow (our unpublished results – Fig1). While overt metastasis develop in lung and LN (48, 49), 10-40% of animals carry occult or small numbers (<10^2 cells) of DTCs in BM, spleen or liver. However, if p38α/β is systemically inhibited, DTCs are detected and metastasis proceeds even in these growth-restrictive sites (our unpublished results – Fig1). This suggests that activation of p38 and/or other stress signals might curtail DTC expansion. In fact, DTCs recovered from the BM but not lung, when re-injected in vivo, remained dormant for at least 6 weeks, suggesting a reprogramming driven by the microenvironment. Unlike HEp3 DTCs derived from lungs, BM-derived DTCs displayed a low ERK/p38 signaling ratio and induction of BHLHB3/41/Sharp-1, NR2F1 and p53 (our unpublished results – Fig1). BHLHB3 was also found to function as a metastasis suppressor in MDA-MB-231
breast cancer cells when mutant p53 function was eliminated (50). In addition, studies on solitary dormant breast DTCs revealed that an enriched collagen-I microenvironment in the lung triggered intravenously delivered tumor cells to exit from dormancy (38). On the other hand environments rich in fibrillar collagen-I were shown to induce quiescence of melanoma cells via activation of the discoidin domain receptor 2 and p15INK4b induction (12). These results imply that stress signaling induced either by therapies or by a restrictive (i.e. fibrotic or non-fibrotic target tissues depending on the tumor type) tissue microenvironments could activate dormancy (or its interruption) in DTCs sustained in part by an ERK\textsubscript{low}/p38\textsubscript{high} ratio even if they carry dominant mutations (i.e. B-Raf) like in melanoma cells.

**Survival of Dormant Tumors Cells.** The fact that quiescent DTCs survive for long periods suggests that survival mechanisms are uncoupled from proliferation signaling. It can be argued that analysis of quiescent tumor cells might provide leads about these survival signals. For instance, cell lines derived from breast cancer patient BM DTCs displayed, as reported for dormant D-HEp3 cells (5, 49) (**Fig1**), upregulation of UPR genes like Grp78 and Grp94 (51) and Grp78 upregulation is usually a poor prognosis marker in carcinomas including breast (52). The UPR attenuates protein synthesis and induces concomitant G\textsubscript{0}-G\textsubscript{1} growth arrest and survival via the up-regulation of genes that promote adaptation to cellular stress (39). However, these cellular outcomes are not necessarily coupled (53).

Additional studies proposed that p38\textsubscript{α/β} upregulated the ER chaperone BiP/Grp78, which inhibited Bax activation and rendered dormant HEP3 cells highly resistant to chemotherapy (54). Further analysis of p38\textsubscript{α} targets in the UPR pathway revealed that dormant tumor cells have a persistent activation of the UPR TF ATF6\textsubscript{α} (42). High expression levels of ATF6 correlated with poor prognosis in HNSCC patients (42), suggesting that dormant tumor cells overexpressing ATF6 may have a survival advantage. Importantly, we found that ATF6\textsubscript{α} transcriptionally induced the small GTPase Rheb to transduce survival signals ((42) and unpublished results – **Fig1**). This small GTPase in turn activated mTOR and downstream S6K and S6RP phosphorylation but this is independent of Akt activation (42). RNAi to ATF6\textsubscript{α} or Rheb was sufficient to induce apoptosis of dormant D-HEp3 cells and eradicate them during their quiescence phase (42). Thus, unlike BiP, ATF6\textsubscript{α} activates an alternative pathway to mTOR signaling that bypasses the need for growth factor and Akt signaling and serves as a basal survival factor required for adaptation to *in vivo* microenvironments. Supporting the existence of quiescence-specific survival signals, the kinase Mirk/Dyrk1B protects quiescent pancreatic tumor cells from reactive oxygen species (55). The transcription factor HES-1, a target of Notch signaling, has also been implicated in repressing oncogene-induced senescence and
differentiation programs while promoting quiescence (30). This suggests that growth-arrested tumor cells might activate quiescence-specific survival mechanisms that render them resistant to micro-environmental and genotoxic stress. Inhibition of these alternative survival pathways could be exploited to induce cell death in quiescent DTCs.

**Clinical – translational advances.** Our knowledge on how the biology and genetics of DTCs influence dormancy and progression is limited. In consequence there are no available dormancy inducing or dormant cell killing drugs. Nevertheless, several translational or clinical applications can be envisioned. One is the necessary characterization of the dormant DTCs to identify the mechanisms driving dormancy. The other is determining whether current therapies can be applied to maintain dormancy of residual disease. In the first case major basic-translational research effort must go into “information-gathering” by characterizing DTCs during asymptomatic periods both in the laboratory and in patients (56, 57). Further, better pre-clinical models must be developed to reproduce the kinetics of disseminated residual disease in patients. Harnessing single-cell profiling technologies (7, 58) to study DTCs in an unbiased manner will also shed light into the genetics and epigenetics of DTC behavior and whether available targeted therapies could be applied, or not, to dormant tumor cells. An excellent review by Chambers and Goss highlights this latter possibility (59). For example, in ER+/PR+ breast cancer recurrences continue to develop after the initial 5 years of conventional anti-estrogen treatment. Among different clinical trials that are described for different cancer types, several clinical trials showed that following a 5-year treatment with tamoxifen for these breast tumors, treatment with the aromatase inhibitor (Letrizole) has additional benefit by further delaying recurrence with treatment schedules spanning >5 years (59). Interestingly, tamoxifen treatment can activate p38 signaling and quiescence (60), suggesting that these “dormancy” therapies might tap into some of the mechanisms described here. This strategy could be considered a maintenance therapy that prevents DTCs from exiting a state of growth arrest (i.e. dormancy maintenance) or by inducing growth arrest (i.e. dormancy induction). However, such a strategy might select for ER-negative tumor cells (59). This may be due to the fact that in order to induce a program of quiescence simply inhibiting mitogenic signaling (i.e. RTK, Raf or Mek1/2 inhibitors) will not be sufficient. Perhaps, in addition, activation of stress signals like p38 or downstream TFs (or others) might be crucial to achieve a long-term stable dormant phenotype (16). In cutaneous but most prominently uveal melanoma late recurrences have been described (12). Although the association between genetics and time to recurrence is not abundant a small study showed that that longer disease-free survival periods were associated with B-Raf but not N-Ras mutations (12). Thus, it is possible that in certain patients, B-Raf+ residual melanoma cells might be kept “dormant” by treating
the patients during asymptomatic conditions with the B-Raf or Mek1/2 inhibitors. If this is the case perhaps other small molecule inhibitors like lapatinib, sorafenib or antibody-based therapies (i.e. herceptin) used to treat other cancers might be useful in maintaining residual disease by treating patients during asymptomatic periods. This approach might keep cells from interrupting dormancy but will not eliminate the quiescent DTCs. Thus, ultimately specific targeting of dormant tumor cells might come only from a full molecular description of these cells. An important example of how analysis of DTCs might provide information different from that obtained from primary tumors came from studying DTCs in esophageal cancer (7). This work revealed that DTCs displayed frequent Her2/neu amplification and this significantly correlated with poor prognosis (7). This information could not be derived from primary tumor analysis and opens the possibility of treating disseminated disease in this type of cancer with therapies already available (i.e. herceptin, lapatinib) originally for breast cancer. The most successful clinical trial would be that testing a drug targets dormant tumor cells while quiescent (5). Unfortunately specific drugs to achieve this goal are currently unavailable and they might be identified only after we understand how therapy and micro-environmental cues influence DTC quiescence and survival. The prevalence of p38 signaling as a negative regulator of cancer progression and as an inducer of dormancy has additional significance. Inhibitors of p38 (such as SCIO-469, RO4402257, PH-797804, SB681323 and BMS-582949) are currently in clinical trials for several neoplastic and non-neoplastic diseases (e.g., hematological malignancies, asthma, neuropathic pain, atherosclerosis, rheumatoid arthritis, etc; www.clinicaltrials.gov and Table 1). Thus, understanding how p38 inhibitors might carry an inherent risk for a proportion of patients with cancer, with predisposition to cancer, or with other diseases is of crucial importance as inhibition of this pathway may fuel cancer progression and metastasis in these patients.

It will be important to determine whether the genes that define growth vs. dormancy in the different experimental models (16, 32, 38, 41, 42) are present or absent in DTCs and how this correlates with clinical progression in patients. For example are the levels of P-ERK1/2 and P-p38 informative of patient prognosis when detected in DTCs? Detection of markers in CTCs might be informative because they might carry like primary tumors some prognostic information. However, DTCs after primary tumor removal are already in target organs and their analysis might provide a more relevant tumor cell population to study because it also incorporates the crosstalk of these DTCs with the microenvironment. Patients with BM DTCs usually have worse prognosis than those without DTCs and their presence reports for metastasis development but not necessarily in the BM, suggesting even more that they can serve as a reporter population even for cancers that do not metastasize in bone (5). For those patients that have BM DTCs, do the dormancy markers discriminate patients with different metastasis-free periods? Do DTCs detected at the time of surgery vs. those detected during disease-free periods or after relapse differ in the expression of dormancy markers?
markers? The findings that lung fibrosis (38) interrupts dormancy of DTCs, suggests also that monitoring the composition of the target organ in specific cancers may predict relapse in certain patients. Thus, a short term translational or clinical benefit from studying DTCs will be the identification of markers to classify patients with dormant (protractedly non-productive (1)) or active (productive) disseminated disease. These markers would be target organ microenvironment- (i.e. collagen-I fibrotic tissues (38)) and DTC-derived. Moreover, the combinatorial use of drugs that modify stromal cells in the target organ microenvironment, for example macrophages that might support metastatic growth (35), may add further advantages to the treatment. The challenges are big and studying DTCs and dormant disease is a difficult task, but the benefits of these efforts should be of great impact for cancer patients.

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**Figure Legend:**

**FIGURE 1.** More general schemes on the mechanisms of tumor cell dormancy can be found in the following references (5). Here we focus on data limited to the role of the ERK1/2 and p38α/β pathways. **Left section.** Depiction of the signaling pathways discovered in a model of aggressive tumor cell (HEp3) reprogramming into quiescence. **In vitro** expansion of primary HEp3 tumor cells (Proliferative tumor cells) leads to their reprogramming into a dormancy program (Dormant tumor cells). A key-signaling feature of these dormant tumor cells is low ERK1/2 and high p38α activation. The resulting ERKlow/p38high ratio induces G0/G1 arrest controlled by the upregulation of p53 (R213Q), NR2F1 and BHLHB3 and by the downregulation of FOXM1 and c-Jun, TFs that promote G1-exit. These signals are required for dormant HEp3 cells to enter and maintain the quiescence state. Furthermore, p38α-dependent activation of ATF6α leads to mTOR activation and subsequent basal survival of dormant HEp3 cells entering quiescence **in vivo** (basal survival). The ERKlow/p38high ratio also induces the expression of the chaperone BiP/Grp78 which inhibits Bax activation to prevent apoptosis. But this survival mechanism appears to be operational only in response to added stress such as chemotherapy (adaptive survival). Integration of these three processes (**G0/G1 arrest + basal survival + adaptive survival**) defines the underlying mechanisms for the acquisition of a dormant phenotype. Depending on the context and the presence of for example metastasis suppressor genes these hallmarks might be regulated by different mechanisms. In contrast, in primary proliferating tumors or tumors exiting dormancy, the ratio is reversed and the resulting ERKlow/p38high ratio switches cell signaling to promote a proliferation phenotype. **Right section.** This section depicts the potential scenarios where dormancy (**G0/G1 arrest + basal survival + adaptive survival**) or proliferative programs might be activated. In primary expanding tumors a proliferative
scenario prevails and tumor cells are able to disseminate carrying this cell signaling profile. One scenario proposes that as these cells reach a growth-permissive target tissue microenvironment (e.g. lung) a proliferative phenotype prevails and dormancy is prevented. In contrast, in growth-restrictive sites such as the bone marrow a dormant phenotype prevails (G0/G1 arrest + basal survival + adaptive survival). This latter scenario presupposes that DTCs are responsive to cues from the tissue microenvironment that can modulate dormancy. It is possible that perturbations of the tissue microenvironment (i.e. irradiation) or the presence of specific stromal cells such as macrophages (not depicted) that lead to tissue remodeling and crosstalk with tumor cells might interrupt dormancy leading to metastasis.

**Table I.** Summary of some of the ongoing clinical trials where small molecule inhibitors of p38 are being used. For more information on these and other trials please follow the provided link.
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<th>Condition</th>
<th>Drug</th>
<th>Phase</th>
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<tr>
<td>Multiple Myeloma</td>
<td>SCIO-469</td>
<td>Phase II&lt;sup&gt;1&lt;/sup&gt;</td>
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<tr>
<td>Bone Marrow Diseases; Myelodysplastic Syndromes; Hematologic Diseases;</td>
<td>SCIO-469</td>
<td>Phase I&lt;sup&gt;1&lt;/sup&gt;</td>
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<tr>
<td>Reumatoid Arthritis</td>
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<td>Phase II&lt;sup&gt;1&lt;/sup&gt;</td>
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<td>Acute Respiratory Ditress Syndrome (ARDS)</td>
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<tr>
<td>Atherosclerosis</td>
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www.clinicaltrials.gov
<sup>1</sup>This study has been completed.
<sup>2</sup>This study is currently recruiting participants.
Clinical Cancer Research

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